## REMARKS

Status of the claims

Claims 1-15, 17-34, and 36-43 are pending and under consideration in this application. After entry of the amendments made herein, claims 1-9, 11, 12, 15, 17-25, and 36-43 will be pending and under consideration in this application, claims 10, 13, 14, and 26-33 having been cancelled herein without prejudice to their being considered in a separate application. No new matter is added by these amendments.

Telephone interview

Applicants thank the Examiner and Supervisory Examiner Anne M. Wehbe for their courtesy and helpfulness in a telephone interview with Applicants' undersigned representative on March 11, 2003.

35 U.S.C. §112, first paragraph, rejection

Claims 1-15, 17-34, and 36-43 stand rejected on the grounds that the specification allegedly does not reasonably provide enablement for the claims.

From the comments on page 2, paragraph 2, the Advisory Action of December 4, 2002, Applicants understand that the enablement rejection is largely, at least, based on lack of enablement by the specification of "pathogenic cells" as the cells targeted by the targeting cells of the invention. While not necessarily agreeing with this position, in order to expedite prosecution of the instant application, Applicants have deleted the term "pathogenic cells" in all the claims under consideration and have replaced it with "cancer cells". Moreover all claims specifying pathogenic cells other than cancer cells have been cancelled.

As pointed out in the Supplemental Response filed March 27, 2002, and the telephone interview with the Examiner and Supervisory Examiner Wehbe on March 11, 2003, the combined data from Example 6 of the specification and the declaration of Daniel A. Vallera submitted March 27, 2002, indicate that: (a) both CD4+ and CD8+ T cells are effective as targeting cells *in vivo*; (b) targeting cells producing recombinant fusion proteins containing either interleukin-4 or interleukin-3 as targeting domains were efficacious *in vivo*; (c) both a solid tumor and a disseminated, non-solid tumor were susceptible to therapy by targeting cells;

(d) targeting cells producing a recombinant fusion proteins containing either the DT390 fragment of diphtheria toxin or BAX as targeting domains were efficacious *in vivo*; and (e) targeting cells were efficacious *in vivo* when administered systemically. Moreover, text in Example 2 (page 45, lines 21-24 of the specification) indicates that the same fusion protein produced by the targeting cells employed in the *in vivo* experiment of Example 6 was able to kill *in vitro*, not only the interleukin-4 receptor (IL-4R) expressing myeloid leukemia cells used in Example 6, but also the cells another IL-4R expressing myeloid leukemia (B162) and IL-4R expressing glioma and neuroblastoma cells. Applicants respectfully submit that, in view of the success of the *in vivo* experiment of Experiment 6, one of skill in art reading the cited text from Example 2, would expect that targeting cells of the invention would be useful for the treatment of a wide range of cancer types.

Supervisory Examiner Wehbe indicated in the telephone interview that, in view of the above-described data and the claims being limited to cancer cells species of pathogenic cells, the claims would likely be considered enabled.

In light of the above considerations, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, be withdrawn.

35 U.S.C. §103(a) rejection

Claims 1-33 and 36-43 stand rejected as allegedly being unpatentable over Chan at el. (Blood 86:2732-2740, 1995 ("Chan et al. a"); and Blood 88:1445-1456, 1996 ("Chan et al. b")) in view of Yang et al. and further in view of Chen et al. Applicants respectfully traverse the rejection.

While the definition of an affinity pair in the specification (e.g., on page 6, lines 5-18) excludes an antibody, or a fragment of an antibody, specific for a molecule on the surface of a pathogenic cell (e.g., a cancer cell) from being a targeting domain in the fusion proteins produced by the targeting cells of the invention, Supervisory Examiner Wehbe requested in the telephone interview that we include this limitation in the claims. This has been done.

From the comments on page 2, paragraph 3, of the Advisory Action of December 4, 2002, Applicants understand the Examiner's position to be that the cited art contains the requisite motivation to combine its various disclosures and thereby to teach the instant invention to one of

ordinary skill in the art. Applicants respectfully submit that not only does the art not contain such motivation, it lacks an essential element of the instant claims.

With respect to the latter issue, the two Chan et al. references describe experiments with isolated immunotoxins containing as targeting domains either granulocyte macrophage colony stimulating factor (GM-CSF) or interleukin-3 (IL-3). Neither reference makes any mention of "targeting cells" as the term is used in the instant application, let alone targeting cells with "specific binding affinity for a cancer cell".

The Chen et al. reference describes experiments using recombinant cells to deliver immunotoxins containing a single-chain antibody as targeting domain to animals with tumors. The only T cells used in the experiments of Chen et al. are MOLT-4 cells, which as indicated in the enclosed product description from American Type Culture Collection (ATCC), Manassas, VA (Exhibit A), are human acute lymphoblastic leukemia cells. Such cells would not be expected to have specific binding affinity the relevant tumor cells and, indeed, this concept is not even mentioned in Chen et al. Moreover, the fact that, in *in vitro* experiments described in Chen et al. control MOLT-4 cells "had no significant effects on tumour cells" (page 78, column 2, paragraph 2) is consistent with the MOLT-4 cells lacking specific reactivity to the tumor cells. Thus, the MOLT-4 cells in the experiments of Chen et al. served merely as *in vivo* factories of the relevant immunotoxin and, as such, lack an essential feature of the instant invention.

In the targeting cells of the invention, there are two levels of specificity. The first level of specificity resides in the specific binding affinity of the targeting cells for a molecule or molecular complex on the surface of target cancer cells. Because of this specific binding affinity, the targeting cells of the present invention would be expected to localize to relevant solid tumors or home to sites of disseminated tumors expressing the antigen for which the targeting cells are specific. By so doing, immunotoxic fusion proteins are selectively produced at sites where they are required and undesired non-specific systemic toxic effects are decreased. The MOLT-4 cells employed by Chen et al. lack this first level of specificity and thus lack a critical feature of the instant invention.

The second level of specificity in the targeting cells of the invention lies in the targeting domains of the fusion proteins secreted by the targeting cells. These targeting domains direct the

fusion protein to the surfaces of cells on which there are molecules to which the targeting domains bind.

The Yang et al. reference describes *in vitro* experiments aimed at eliminating virus-, in particular HIV-1-, infected cells and thus its disclosure is not applicable to the tumor-specific targeting cells of the instant invention. The single mention of tumors at the end of the last sentence of the Discussion section of the article can in no way be considered a description of targeting cells having specific binding affinity for target tumor cells. It is not at all clear from the sentence whether the "tumor-specific antigens" referred to in this sentence are antigens to which the targeting domains of relevant immunotoxins could bind or antigens to which targeting cells could bind. The Chen et al. article is authored by the same research group as Yang et al.; indeed Yang and Chen are authors on both articles. Moreover, both articles were published in January, 1997. It is very possible that the authors of Yang et al. contemplated the utility of T cells in cancer (as expressed in the sentence from Yang et al. referred to above) as being the same as that described in Chen et al., i.e., to serve as factories of an appropriate immunotoxin but without a targeting function. However, whatever the intention of the authors of Yang et al., the cryptic reference to tumors in the relevant sentence cannot be concluded to teach the use of targeting cells with significant binding affinity for cancer cells as required by the present claims.

Even if one of skill in the art could conclude the ambiguous sentence in Yang et al. to be disclosing antigen-specific targeting cells for use in the treatment of cancer (a conclusion Applicants believe for the reasons given above to be untenable), the sentence would be considered by such a person to be at best an "invitation to try" without the least assurance of success. This is particularly true in that, not only are the experiments described in the Yang et al. reference not directed to cancer cells, they are all *in vitro*, and thus provide no indication of the *in vivo* utility of even HIV-1-specific, immunotoxin-producing targeting cells, let alone the tumor-specific *in vivo* utility alluded to in the last sentence from the article referred to above.

In addition to not disclosing all the elements of claim 1, the cited articles do not contain the necessary motivation to combine their respective disclosures.

The two Chan et al. references describe experiments with fusion proteins containing DT390 fused to either GM-CSF or IL-3. No mention or even a suggestion of the desirability of using targeting cells of any sort, let alone CD8+ CTL or MOLT-4 (as disclosed in Yang et al.

and Chen et al., respectively), is made by either Chan et al. reference. Thus neither of the Chan references contains the necessary motivation to combine its disclosure with that of Yang et al. and/or Chen et al. and thereby to render obvious the invention specified by the instant claims.

The Examiner is reminded that antibodies and antibody fragments are specifically excluded as targeting domains in the instant invention. Yang et al. and Chen et al. describe experiments using T cells (MOLT-4 or CD8+ CTL, respectively) to deliver immunotoxins using antibody fragments (Fab and single chain Fv, respectively) fused to toxic proteins to HIV-infected cells *in vitro* and tumor cells *in vitro* and *in vivo*, respectively. The two references focus exclusively on the use of antibodies or antibody fragments for use as targeting domains in immunotoxins. There is in neither Yang et al. nor Chen et al. any mention or even a suggestion of the desirability of using targeting domains other than antibodies or antibody fragments. Thus, neither Yang et al. nor Chen et al. contains the necessary motivation to combine its disclosure with that of either or both of the Chan et al. references. and thereby to render obvious the invention specified by the instant claims.

Finally, in that none of cited art shows *in vivo* cancer therapeutic efficacy of targeting cells having specific binding affinity for tumor target cells and secreting fusion proteins containing non-antibody-derived targeting domains, the data obtained in the experiment described in Example 6 showing such efficacy constitute unexpected results.

In light of the above considerations, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) be withdrawn.

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| **ATCC Number:** | **CRL-1582** Order this item | **Price:** | **$175.00** |
| **Designation:** | **MOLT-4** | **Depositors:** | J. Minowada |
| **Biosafety Level:** | 1 | **Shipped:** | frozen |
| **Medium & Serum:** | See Propagation | **Growth Properties:** | suspension |
| **Organism:** | *Homo sapiens* (human) | **Morphology:** | lymphoblast |
| **Tissue:** | T lymphoblast; acute lymphoblastic leukemia | | |
| **Cellular Products:** | high levels of terminal deoxynucleotidyl transferase (TdT) are produced [22735] | | |
| **Permits/Forms:** | In addition to the MTA mentioned above, other ATCC and/or regulatory permits may be required for the transfer of this ATCC material. Anyone purchasing ATCC material is ultimately responsible for obtaining the permits. Please click here for information regarding the specific requirements for shipment to your location. | | |

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| **Comments:** | The line was established from cells taken from a patient in relapse. [22524]<br>The patient had received prior multidrug chemotherapy. [22524]<br>There is a G -> A mutation at codon 248 of the p53 gene. [23322]<br>P53 is not expressed. [23322]<br>The cells do not produce immunoglobulin or Epstein-Barr virus. [22524]<br>**MOLT-4** was derived from the same patient as the MOLT-3 cell line (ATCC CRL-1552). [22524]<br>The line was originally contaminated with mycoplasma but has been cured with antibiotics. |
| **Tumorigenic:** | yes, in untreated nude mice, anti lymphocyte serum treated mice and X-irradiated mice |
| **Antigen Expression:** | CD1 (49%), CD2 (35%), CD3 A (26%) B (33%) C (34%), CD4 (55%), CD5 (72%), CD6 (22%), CD7 (77%) |

| | |
|---|---|
| **Karyotype:** | This is a human cell line with the hypertetraploid chromosome number. The modal chromosome number was 95 occurring in 24% of cells. The rate of cells with higher ploidies was 0.8%. The 6q- and t(7;7) were paired and also common to all cells. The i(17q) was single and occurred only in some cells. Most normal chromosomes had four copies per cell except for the paired N7, X and Y, and two to three copies for N17. |
| **Age Stage:** | 19 years |
| **Gender:** | male |
| **Propagation:** | ATCC medium: RPMI 1640 medium with 2 mM L-glutamine adjusted to contain 1.5 g/L sodium bicarbonate, 4.5 g/L glucose, 10 mM HEPES, and 1.0 mM sodium pyruvate, 90%; fetal bovine serum, 10%<br>Temperature: 37.0 C |
| **Subculturing:** | Cultures can be maintained by addition or replacement of fresh medium. Start new cultures at 4 X 10 exp 5 cells/ml and subculture before the cell density reaches 2 X 10 exp6 cells/ml. |
| **Fluid Renewal:** | Add fresh medium every 2 to 3 days (depending on cell density) |
| **Freeze Medium:** | culture medium 95%; DMSO, 5% |
| **Related Products:** | Recommended medium (without the additional supplements or serum described under ATCC Medium) - ATCC 30-2001<br>recommended serum - ATCC 30-2020<br>derived from same individual - ATCC CRL-1552 |
| **References:** | 22524: Minowada J, et al . Rosette-forming human lymphoid cell lines. I. Establishment and evidence for origin of thymus-derived lymphocytes. J. Natl. Cancer Inst. 49: 891-895, 1972. PubMed: 4567231<br>22550: Ohsugi Y, et al . Tumorigenicity of human malignant lymphoblasts: comparative study with unmanipulated nude mice, antilymphocyte serum-treated nude mice, and X-irradiated nude mice. J. Natl. Cancer Inst. 65: 715-718, 1980. PubMed: 6932523<br>22735: Mertelsmann R, et al . T-cell growth factor (interleukin 2) and terminal transferase activity in human leukemias and lymphoblastic cell lines. Blut 43: 99-103, 1981. PubMed: 6942897<br>23322: Rodrigues NR, et al . p53 mutations in colorectal cancer. Proc. Natl. Acad. Sci. USA 87: 7555-7559, 1990. PubMed: 1699228<br>23337: Sandstrom PA, Buttke TM . Autocrine production of extracellular catalase prevents apoptosis of the human CEM T-cell line in serum-free medium. Proc. Natl. Acad. Sci. USA 90: 4708-4712, 1993. PubMed: 8506323 |



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